Phenotypic Markers of Radiation Sensitivity

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Mans Radiation Burden

Air travel

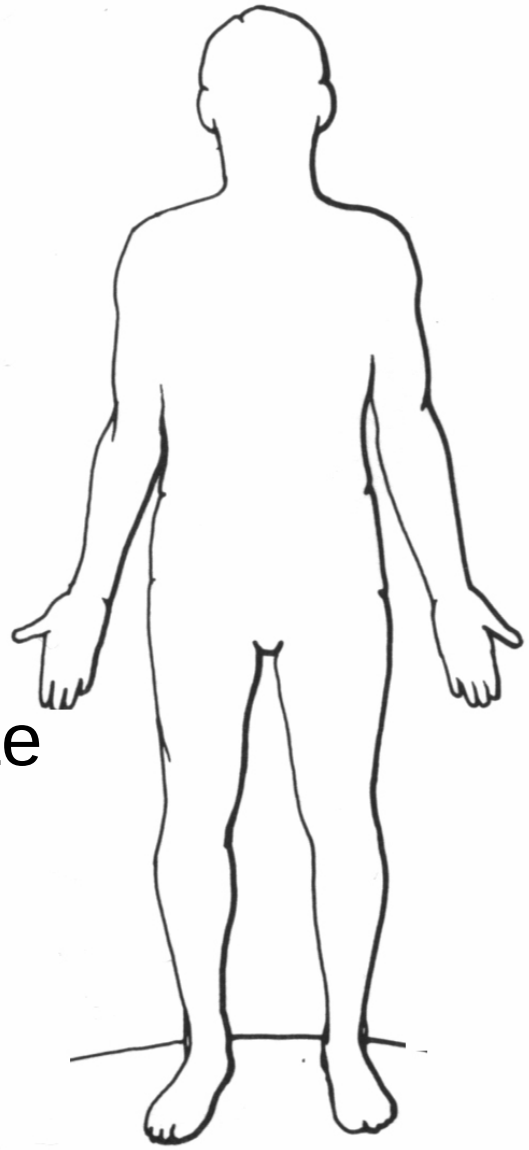
Testing fallout

TV & luminous watches

Nuclear power plants (20%)

Radioactive waste

Diagnostic & therapeutic radiation*



Cosmic rays

Air (radon)

Building material

Water

Food

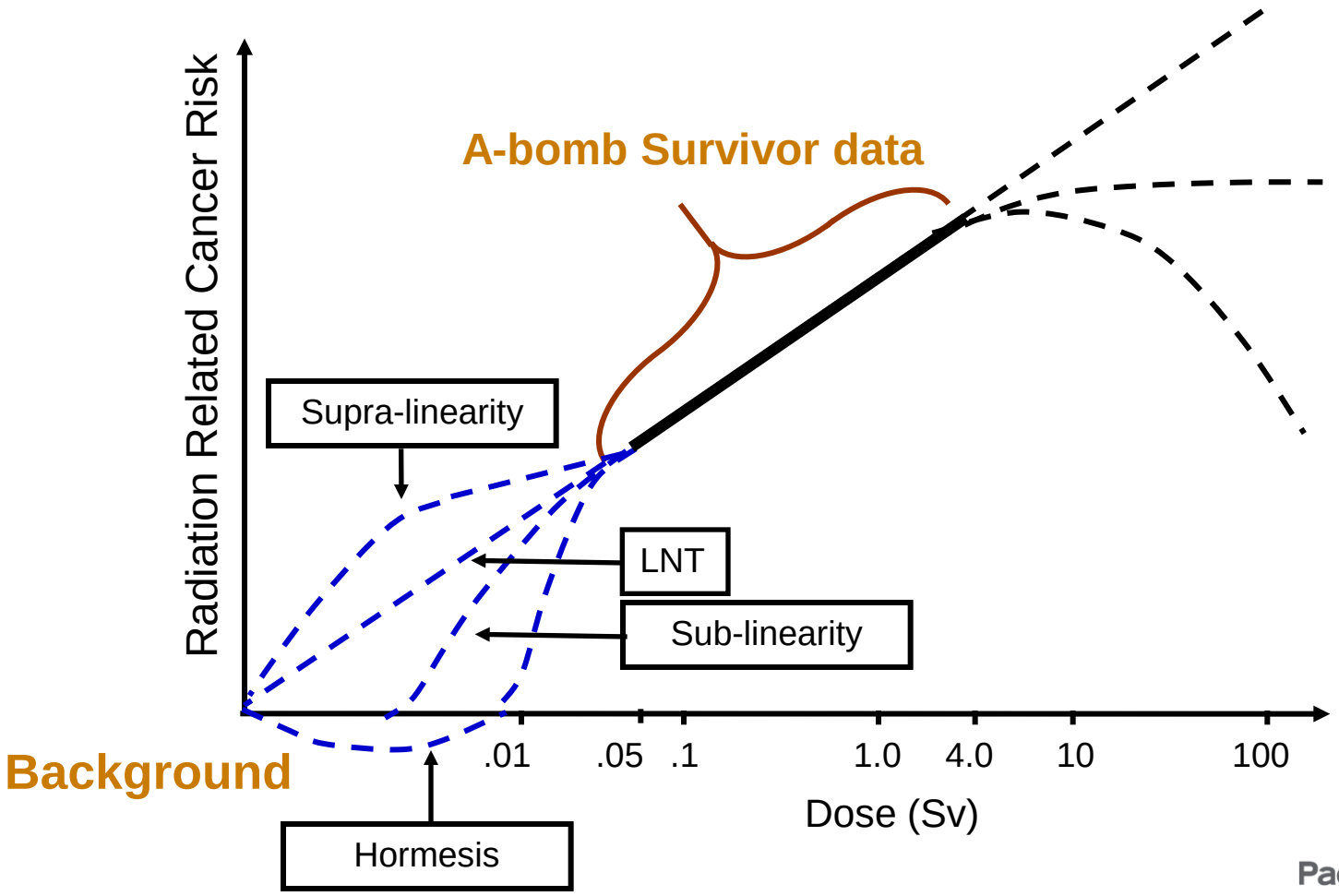
Earth

*> 200 million procedures/year (USA), 2 billion worldwide

Everybody knows radiation causes detrimental effects:

When asked “is a low dose of radiation safe?”
will you say “YES”?
or will you say
“There is always the possibility of a detrimental effect but at low doses it’s **very very** small”

The dilemma for radiation protection: what is the scientific basis for radiation standards to protect the public from exposures to low levels of ionizing radiation (<0.1 Sv) where there are considerable uncertainties in the epidemiological data.



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Radiation Protection Considerations

Science is only one input to risk management

What are the other inputs?

Tradition

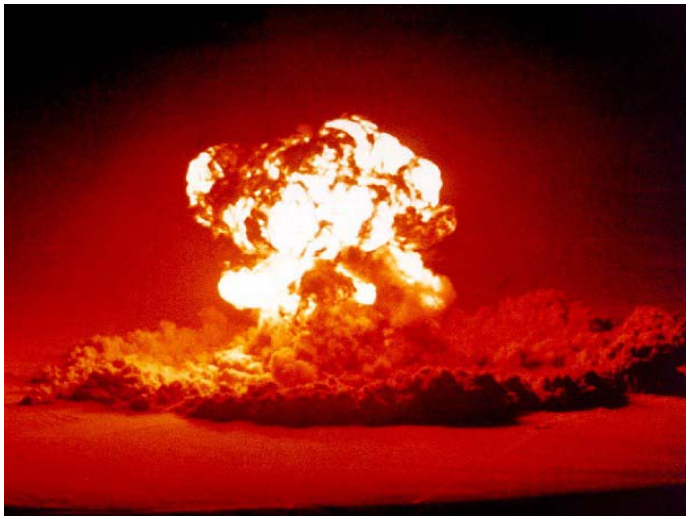
Not scaring people

Politics

Social values

Economic considerations

Technological considerations



We have a long legacy of mistrust to deal with!

Plus some widely diverging opinions

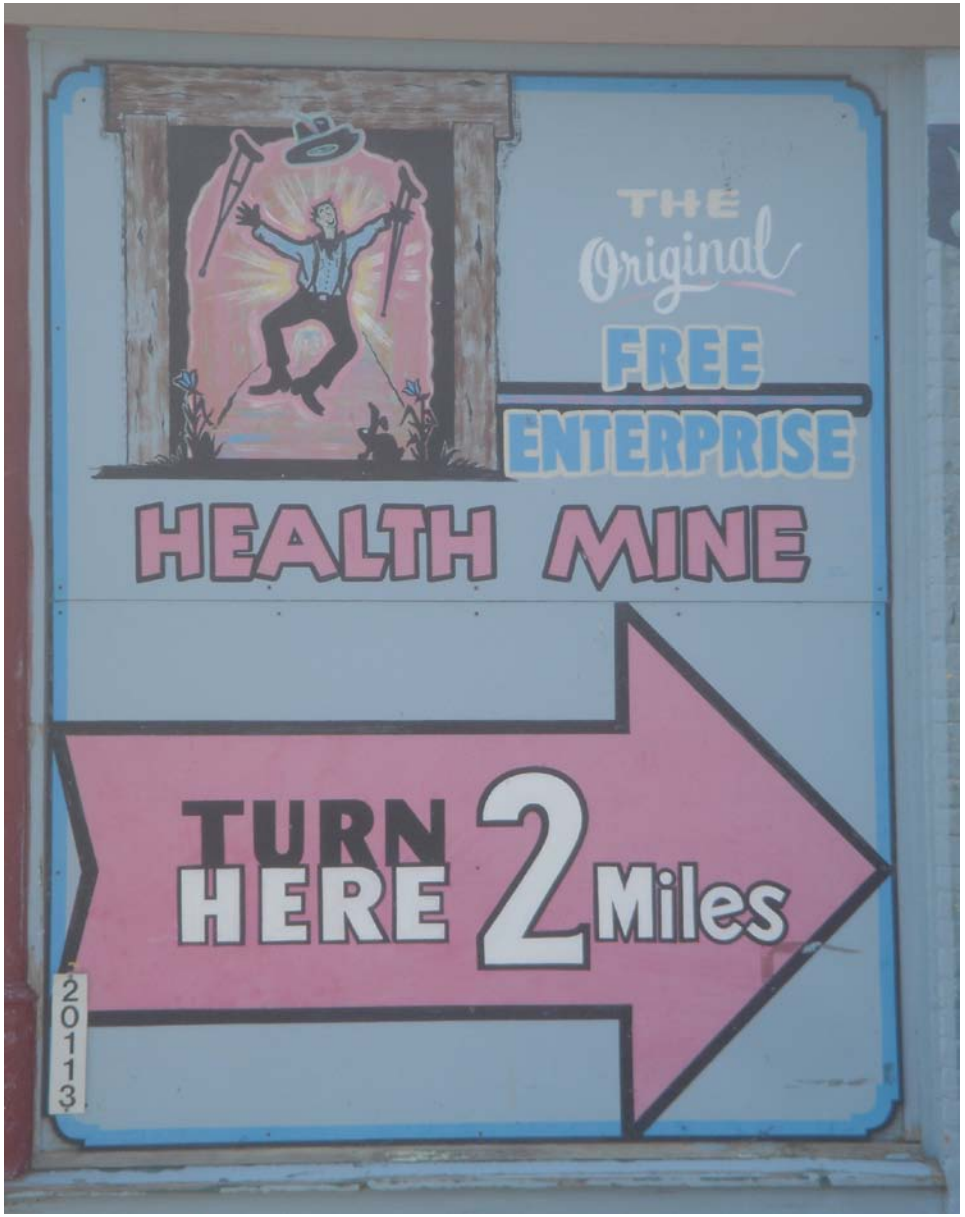
Hormesis - tolerance - acceptance - total denial

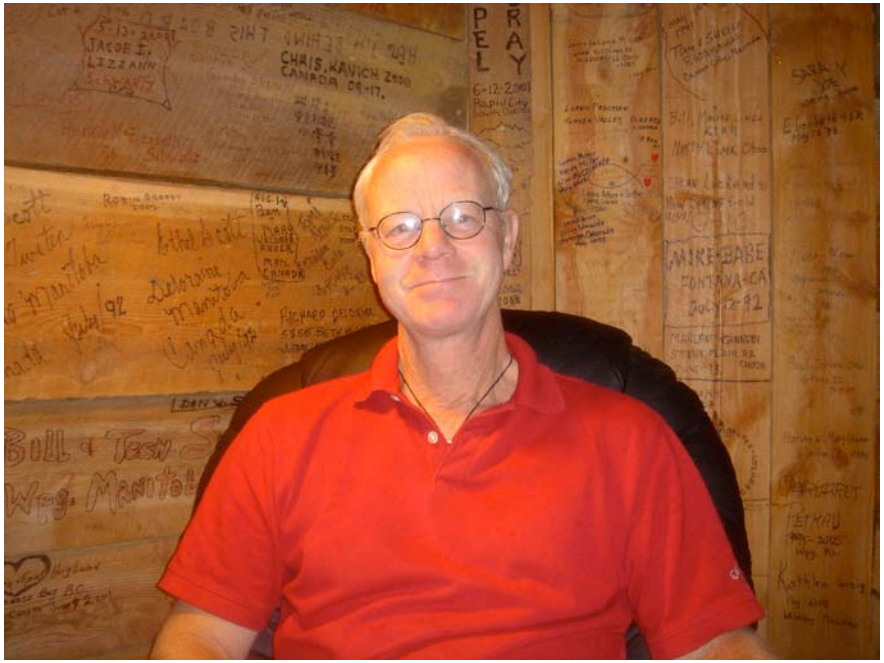
Remember - We All Have Different Perception of Risk

STEPHANIE KLEIN-DAVIS | The Roanoke Times

Mellisa Williamson, 35, a Bullitt Avenue resident, worries about the effect on her unborn child from the sound of jackhammers.

On the other hand - complex biological systems have physiological barriers against damage and disease. Primary damage linear with dose, secondary damage not. Cellular processes block damage propagation to clinical disease.





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Linear Non-Threshold is a Model/Hypothesis:

As such it has been used and abused!

Goal: public and worker protection

Assumes: Correctly that

- Tissues/organs differentially sensitive
- Risk varies with
  - Age
  - Sex
  - Socio economic status
  - Diet and lifestyle
  - Genetic makeup and race
  - Dose and dose rate
  - Radiation quality

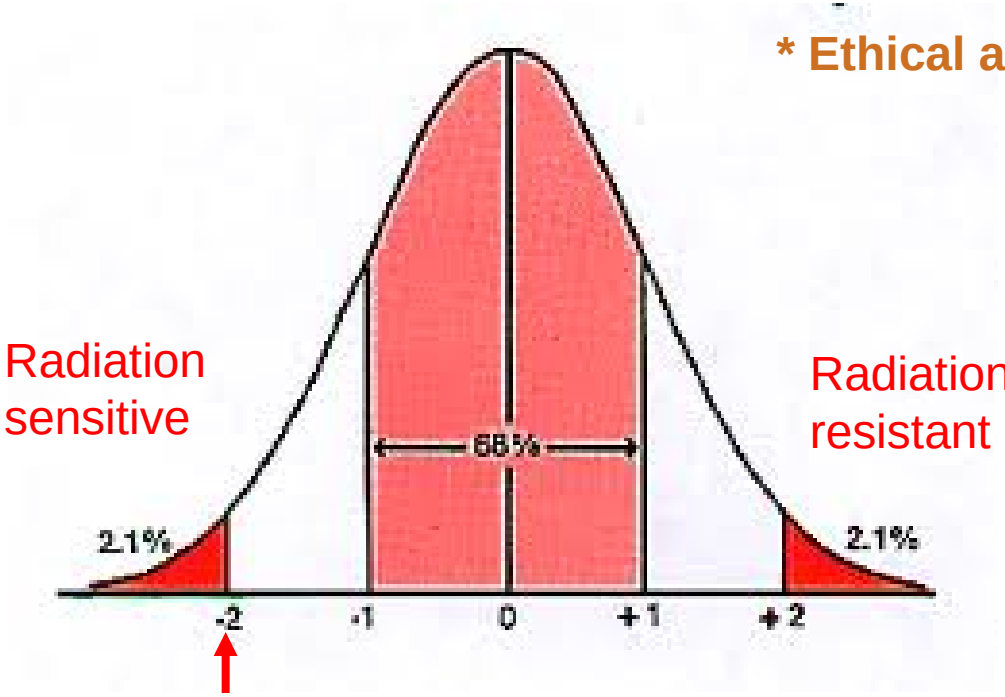
Questions: How to design a system that limits risk?
How do we assign a potential human health risk?

Caveats: This system must take into account :

The most sensitive organ (breast)*?

The most sensitive individual*?

*** Ethical and legal questions**



Where do you draw this line for regulatory purposes?

www.usatoday.com THE NATION'S NEWSPAPER 50 CENTS

FINAL SPORTS

Super Bowl

Let the hype begin

Clock is ticking toward Sunday. Full report, 1-4C
- 10 years ago, war was on our minds, 1C
- Coming Friday: Bonus Section

USA TODAY

NO. 1 IN THE USA

The Golden Globes

'Gladiator' wins best drama film

Julia Roberts, Tom Hanks honored for drama roles; *Almost Famous* named best comedy film ■ 1-2D
- The red carpet, 5D

Roberts: Smiles for *Erin Brockovich*.

Monday, January 22, 2001

Newsline

■ News ■ Money ■ Sports ■ Life

usatoday.com's new look

Get the latest news, stocks, scores and more right now at USA TODAY's 24-hour online news site, all with a clean new interface. Plus, a stand-alone Tech section.

■ Asia stocks mixed overnight

Japan's Nikkei average is down 137 points, 1.0%, to 13,852 early today. Hong Kong's Hang Seng index is up 136 points, 0.9%, to 16,069.

CT scans in children linked to cancer later

By Steve Sternberg
USA TODAY

Each year, about 1.6 million children in the USA get CT scans to the head and abdomen — and about 1,500 of those will die later in life of radiation-induced cancer, according to research out today.

What's more, CT or computed tomography scans given to kids are typically calibrated for adults, so children absorb two to six times the radiation needed to produce clear images, a second study shows. These doses are "way bigger than the sorts of doses that people at Three Mile Island were getting," David Brenner of Columbia University says. "Most people got a tenth or a hundredth of the dose of a CT."

Both studies appear in February's *American Journal of Roentgenology*, the nation's leading radiology journal. The first, by Brenner and colleagues, is the first to estimate the risks of "radiation-induced fatal cancer" from pediatric CT scans. Until a decade ago, CT scans took too long to perform on children without giving them anesthesia to keep them still. Today's scanners spiral around the patient in seconds, providing cross sections, or "slices," of anatomy.

Doctors use CT scans on children to search for cancers and ailments such as appendicitis and kidney stones.

"There's a huge number of people who don't just receive one scan," says Fred Mettler of the University of New Mexico, noting that CT scans are used for diagnosis and to plan and evaluate treatment. "The breast dose from a CT scan of the chest is somewhere between 10 and 20 mammograms. You'd want to think long and hard about giving your young daughter 10 to 20 mammograms unless she really needs it."

Mettler recently published a study showing that 11% of the CT scans at his center are done on children younger than 15, and they get 70% of the total radiation dose given to patients. Children have more rapidly dividing cells than adults, which are more susceptible to radiation damage. Children also will live long enough for cancers to develop.

Researchers led by Lane Donnelly at Cincinnati's Children's Hospital found that children often get radiation doses six times higher than necessary. Cutting the adult dose in half would yield a clear image and cut the risk a like amount, Brenner says. "Radiologists genuinely believe the risks are small," he says. "I suspect they've never been confronted with numbers like this."

Brenner & Hall; "Computed tomography - An increasing source of radiation exposure" NEJM 357, 2277-2284 (2007)

Scott, Sanders, Mitchel & Boreham; "CT scans may reduce rather than increase the risk of cancer" J. Amer. Phys & Surg. 13, 8-11 (2008)

What About in the Low Dose Region?

BEIR VII

Académie des sciences
INSTITUT DE FRANCE

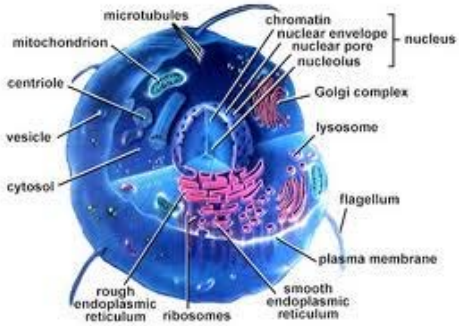
BEIR VII cited 1386 peer reviewed publications

French Academie des Sciences cited 306 publications

Overlap in publications cited = 68

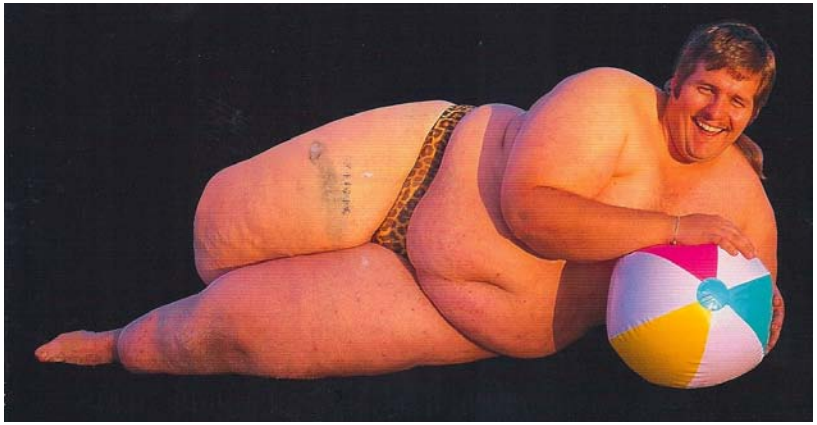
Extrapolation from experimental systems:

Cells → tissues → organs → humans



What does *in vitro* cell culture tell us about a response in humans?

What do *in vivo* models tell us about a response in humans - how do you extrapolate from an an animal model to the human population? Should you?



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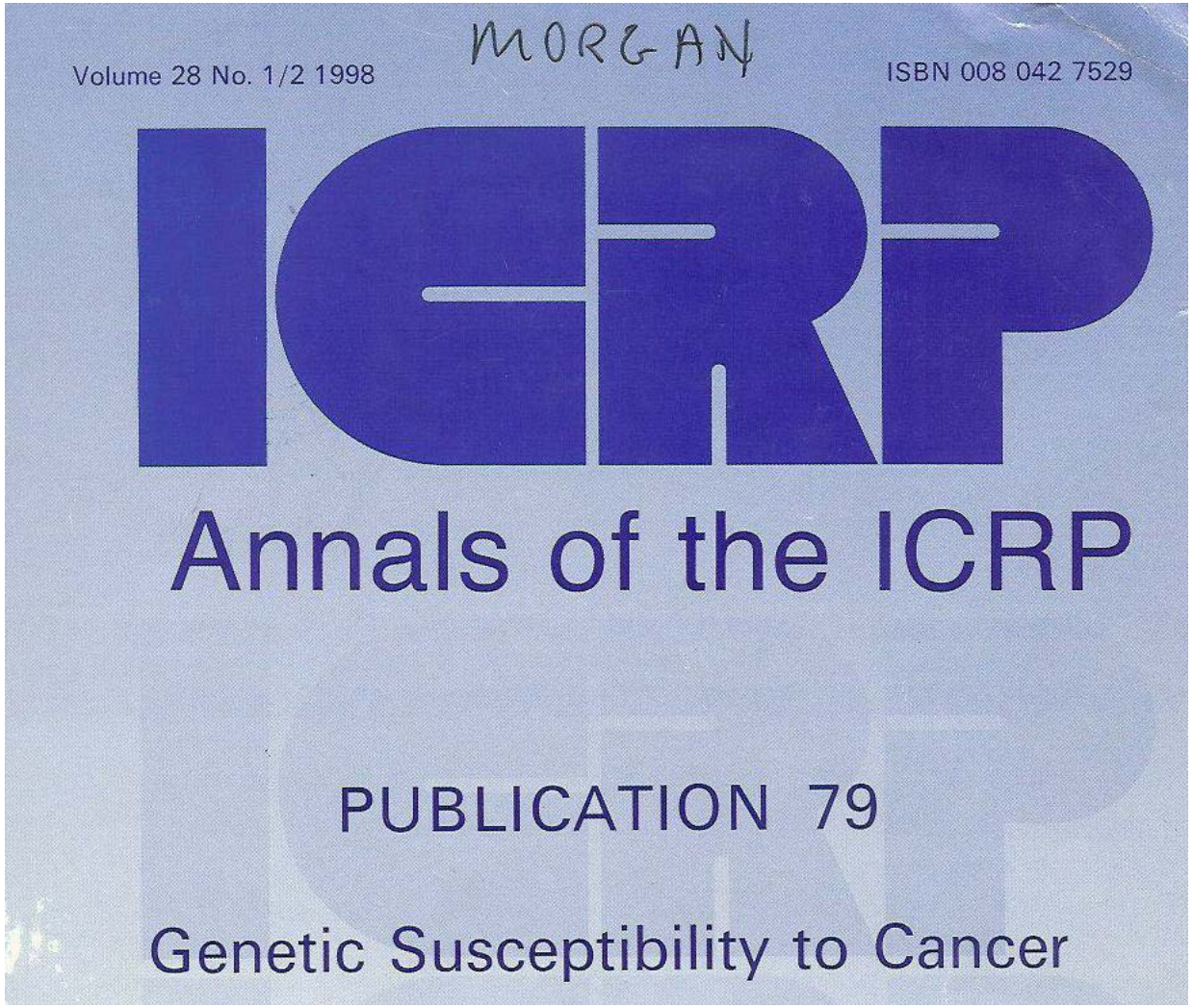


Task Group met 1993 - 1996; report adopted by the Commission 1997; published 1998

Genetic Biomarkers of Therapeutic Radiation Sensitivity

Occurrence of acute or late normal tissue reactions after therapeutic radiotherapy and cellular responses in *in vitro* radio-sensitivity assays do not correlate well.

No one test suitable of predicting the risk of severity of such reactions

Some interesting correlations but no genetic factors that might specifically influence occurrence of adverse reactions identified to date.

Associations between common polymorphisms in DNA damage detection and repair and development of adverse reactions to radiotherapy?

Small numbers of individuals showing either early or late reactions have been studied. **Large cohorts will be necessary**.

SNPs to be studied should include genes involved in

- DNA damage detection and repair (ATM, BRCA 1/2)
- pro-fibrotic and inflammatory cytokines (TGFβ1)
- endogenous anti-oxidant enzymes
- general metabolism and homeostasis

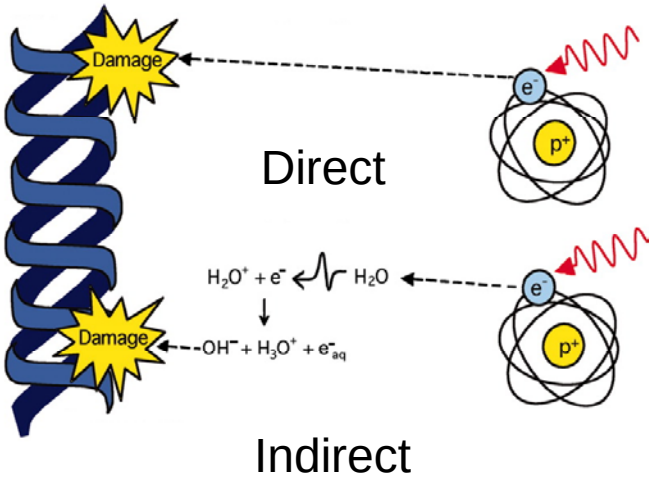
One gene polymorphism or combination of genes and polymorphisms?

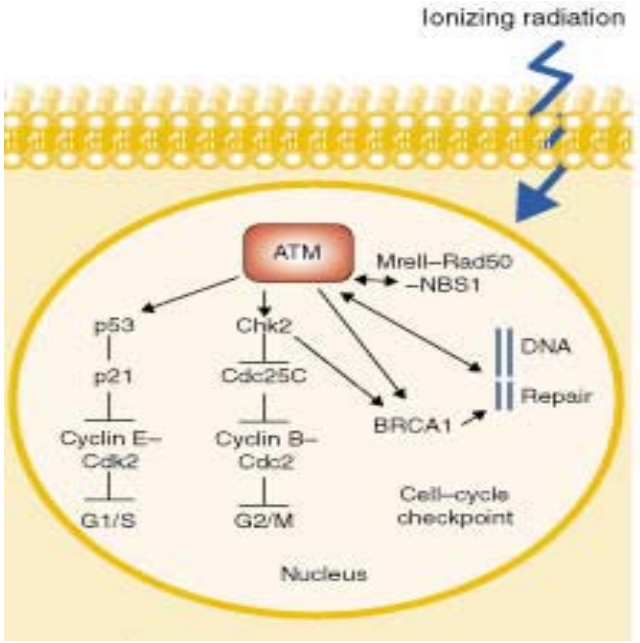
Cellular and Molecular Factors that Modulate Sensitivity to Ionizing Radiation.

Damage recognition processes
Damage repair
Damage signaling pathways
Antioxidant status
Cell cycle and cell cycle checkpoint control
Regulation of apoptosis
Cellular homeostasis
Target tissue/organ
Age at exposure
Gender

Total dose
Dose rate
Radiation quality
Dose distribution
Mode of exposure - internal and/or external
Time since exposure

Multi-cellular organisms have protective mechanisms beyond those available to individual cells or organelles.





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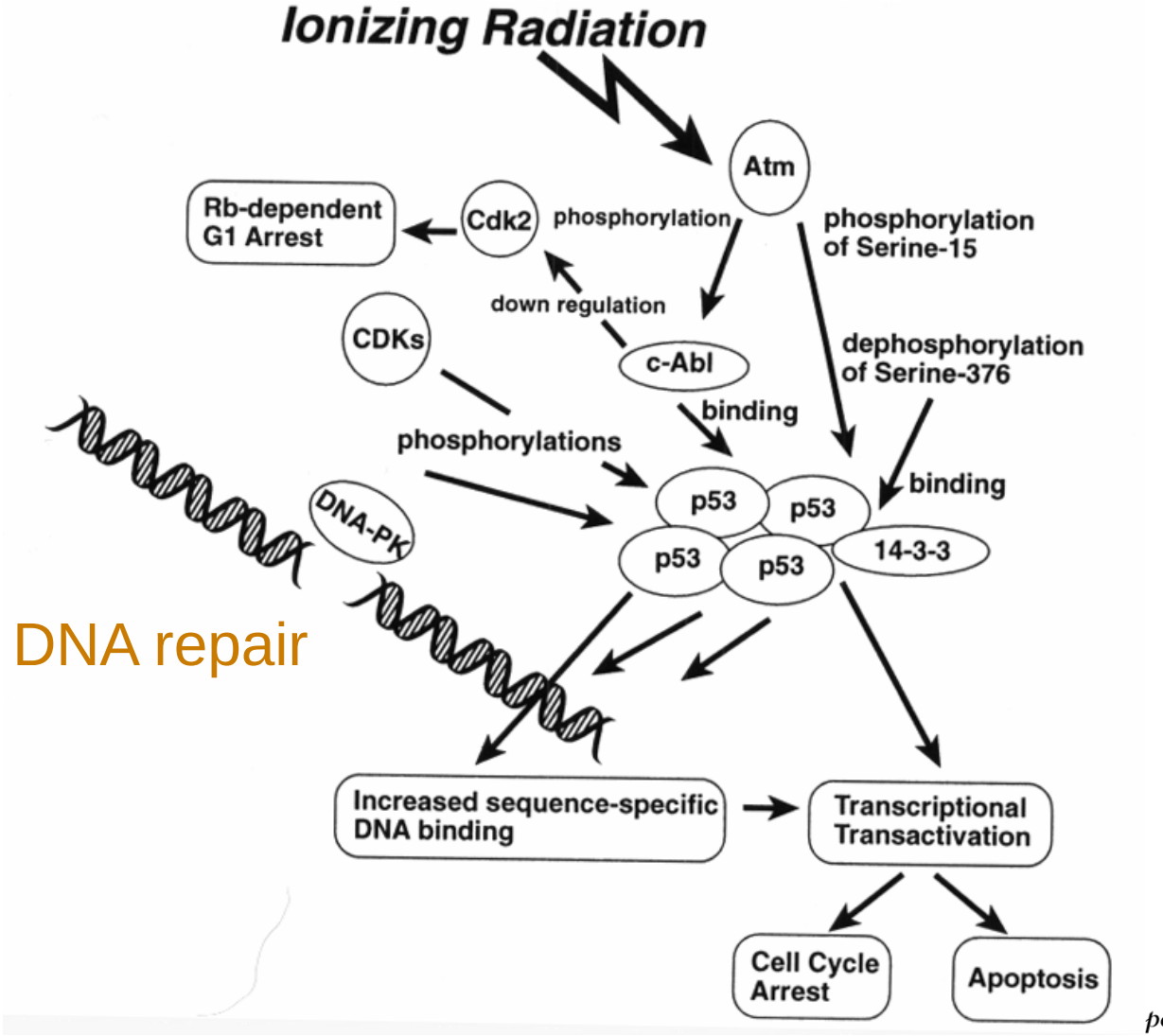
What Influences Cellular/Tissue/Organ Response?

Damage induced signal transduction

Mammalian cellular stress response



Radiation sensitivity in normal humans

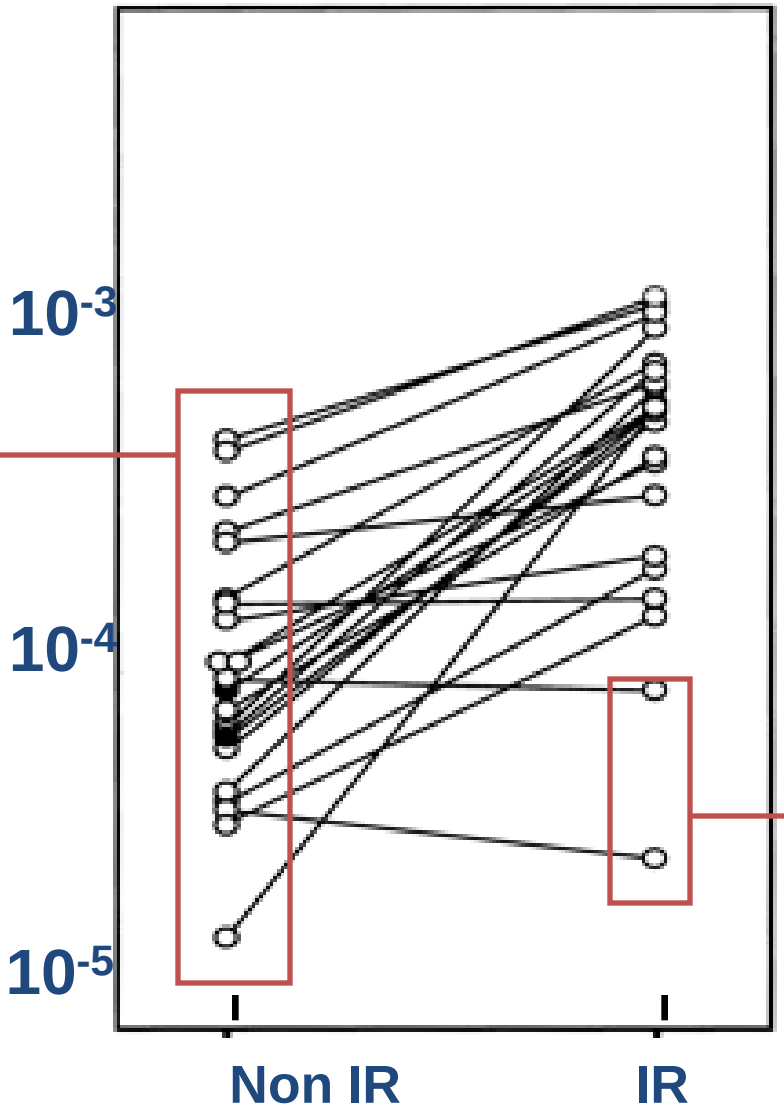
Table 2.4. Radiosensitivity of fibroblasts and lymphocytes from sets of normal human donors[a]

Number of donors	Range of D10 (cGy)	Cell type[b]	References
42	230–380	F	Cox and Masson (1980); Thacker (1989)
15	145–180	L	Kutlaca *et al.* (1982)[c]
10	350–450	F	Nagasawa and Little (1988)
6	300–360	F	Arlett *et al.* (1988)
24	196–372	F	Little *et al.* (1988)
21	213–448	F	Paterson *et al.* (1989)
56	210–370	F	Ban *et al.* (1990)[d]
31	180–420	F	Little and Nove (1990)
22	253–404	F + L	Kurshiro *et al.* (1990)[d]
33	220–390	F + L	Green *et al.* (1991)
32	320–410	L	Nakamura *et al.* (1991)[d]
8	498–295	L	Geara *et al.* (1992)
6	446–264	F	
32	353–253	F	Begg *et al.* (1993)[d]
5	305–242	F	Wann *et al.* (1994)

ICRP: Genetic Susceptibility to Cancer, publication 79, (1997)

^{137}Cs γ-ray mutagenesis in B6D2 *aprt*+/- kidney cells exposed to 7.5 Gy *in vivo*

Variability in baseline mutation frequency in an inbreed mouse, on a fixed diet - what about the human population?



Ponomareva et al. Cancer Res. 62, 1518-23 (2002)

Decreases just as important / informative as increases

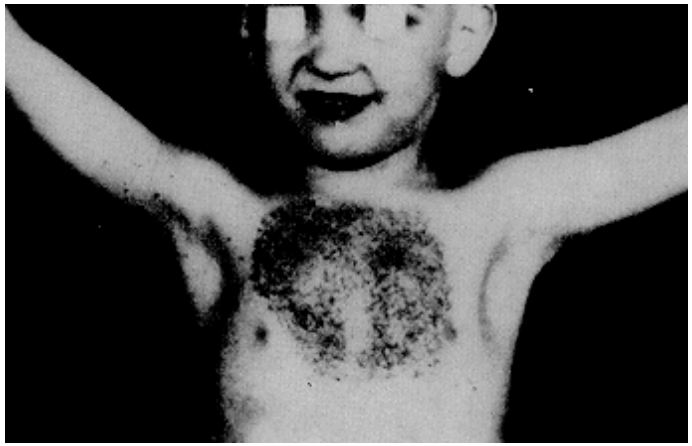
Human Genetic Disorders with Hypersensitivity to Ionizing Radiation

Only ataxia-telangiectasia (AT; ATM), ataxia-telangiectasia-like disorder (ATLD, Mre11), and Nijmegen breakage syndrome (NBS, NBS1) show unambiguous evidence of radiation hypersensitivity to the lethal effects of radiation. Other genetic disorders implicated but likely reflect "technical differences" rather than genetic differences.

Modest radiation sensitivity observed in

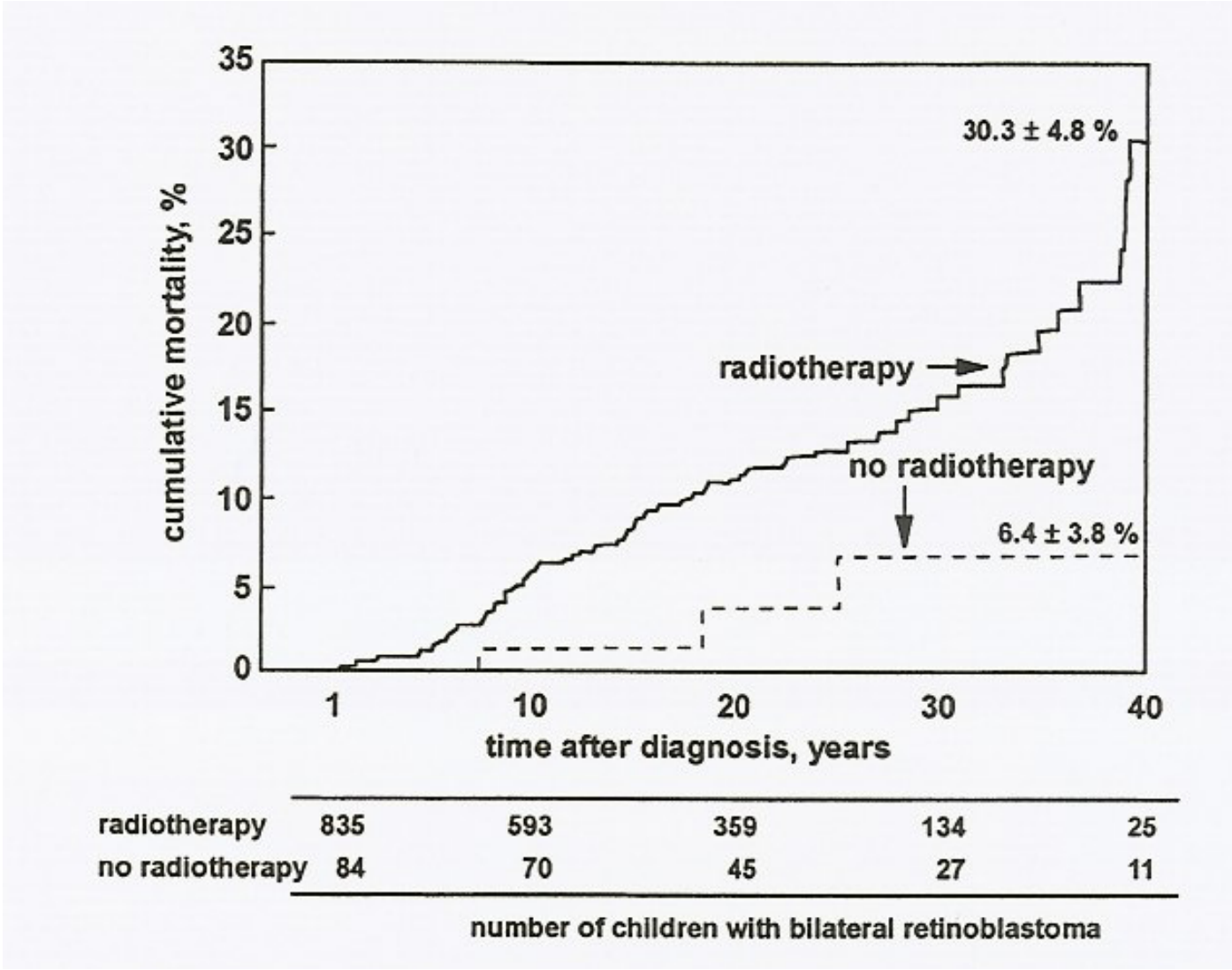
Li-Fraumeni syndrome
retinoblastoma
Nevoid basal cell carcinoma syndrome

Mutations in genes for cell cycle control?



Scharnagel & Pack, Am. J. Dis. Child. 77, 647-651 (1949)

Follow-up of 1603 US retinoblastoma patients treated with radiation - risk of second tumors in heritable (bilateral) RB



Eng et al., JNCI 85, 1121-1128 (1993)

Breast Cancer Risk in AT- or BRCA1/2-heterozygotes

Increased cancer susceptibility in obligate AT+/-

Carriers in population ~1%

General consensus from screening breast cancer cases and controls revealed few mutations in the ATM gene and no significant differences between case and control groups in mutation frequency.

ATM^{trunc} make little or no protein
ATM^{mis} make reduced amount of defective protein

Possible association between ATM and radiation-induced breast cancer is even more contentious. **Consensus - no significant difference**

Likewise, no evidence of increased radiation sensitivity in BRCA1 or BRCA2 heterozygotes, or that BRCA1 or BRCA2 heterozygosity could account for a significant proportion of radiation sensitive individuals.

Relevance of ATM knockout mouse??

Genetic Susceptibility to Radiation Carcinogenesis

Mechanistically - good reason to believe genetically determined risk of spontaneously arising cancer will be accompanied by increased sensitivity to the cancer risks of ionizing radiation.

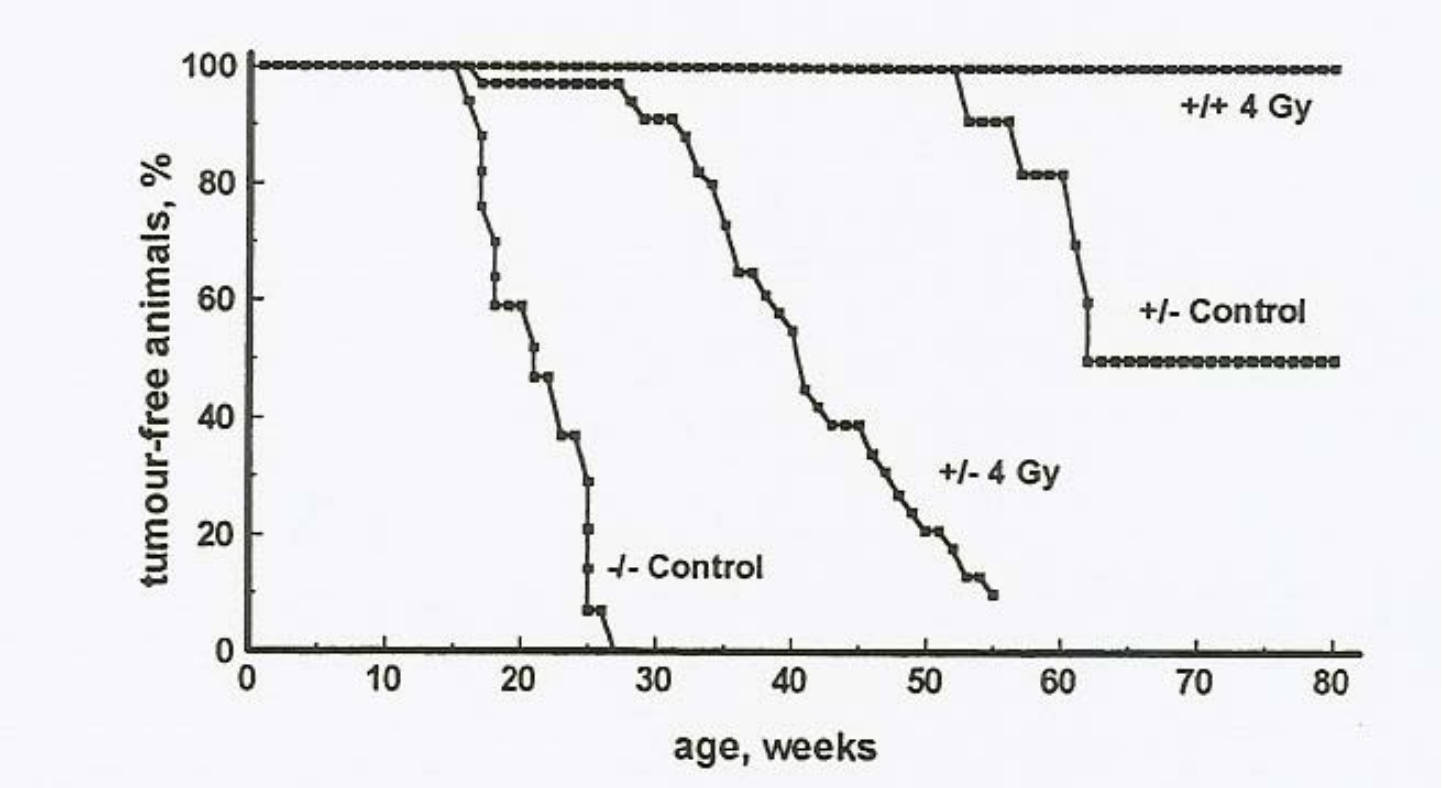
Rodent models of tumor suppressor gene deficiency (heterozygotes, +/-)

Li-Fraumeni syndrome (*p53*-deficiency)
increased tumor incidence, no change in tumor spectrum
Familial adenomatous polyposis (*Apc*-deficiency)
increased intestinal adenomas after whole body irradiation
Tuberous sclerosis (*Tsc2*-deficiency)
increased incidence of kidney tumors after renal irradiation

Rodent models of genes involved in cellular responses to DNA damage

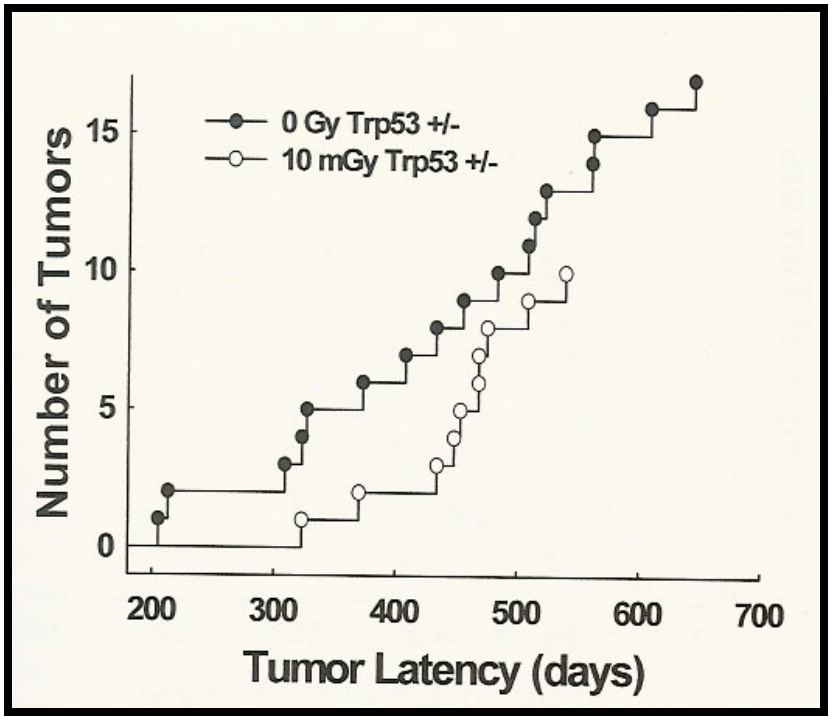
Ataxia telangiectasia (ATM deficiency)
increased sensitivity (survival and premature graying), cataracts
Nijmegen breakage syndrome (NBS1 deficiency)
increased epithelial tumors (thyroid and lung), lymphomas
Familial breast cancer (BRCA1 mutations)
3-5 fold > ovarian tumors, no change in breast cancer or lymphoma. Note: generally high radiation doses

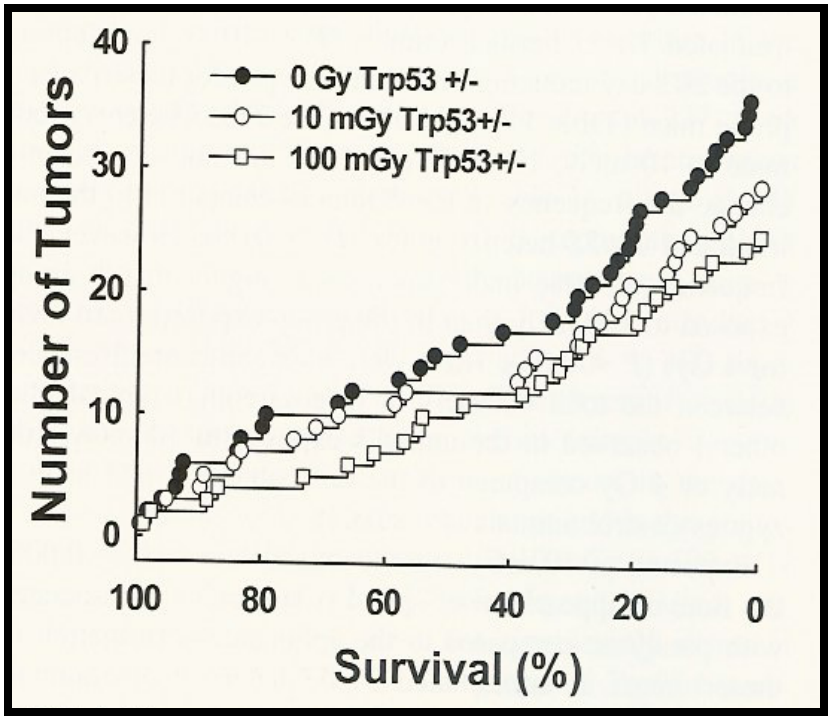
Effects can vary with dose



Kemp et al., p53-deficient mice are extremely susceptible to radiation-induced tumorigenesis. Nature Genetics 8, 66-69 (1994)

Effects can vary with dose





Mitchel et al., Low doses of radiation increase the latency of spontaneous lymphomas and spinal osteosarcomas in cancer-prone, radiation-sensitive Trp53 heterozygous mice. Radiation Res. 159, 320-327 (2003)

Polymorphisms in DNA strand break repair genes and genotoxicity in workers exposed to low dose ionizing radiation [Aka et al., Mutation Res., 556, 169-181 (2004)]

10-15% healthy individuals show reduced (68-80%) DNA repair capacity phenotypes:
OGG1 - glycosolase removes 8-oxo-guanine (BER)
XRCC1 - complexes with polβ, PARP & DNA ligase III to repair single strand breaks
XRCC3 - stabilizes Rad51 to function in HR for DSBs

32 male Belgian nuclear power plant workers (γ-ray doses 15.7 +/- 8.0; range 0.4 - 71.6mSv)
31 non exposed male office staff

Blood genotyped and analyzed for DNA damage, 0 or 2Gy damage (Comet assay) and micronuclei

Results

No statistically significant differences observed
- mean tail length
- tail movement
- MN frequency in bi- or mononucleated cells

Level of each biomarker > exposed v. controls
Residual damage > controls v. exposed
Smokers > damage and MN controls v. exposed

Conclusions

No single genotype predicts IR sensitivity
Combinations?
Cumulative dose of 15.7 ± 8.0mSv did not induce a statistically significant genotoxic effect
Smoking and age significant confounders

Predictors of Response

Radiation induced micronuclei in blood samples from women with advanced stage cervical carcinoma.

Sampled before RT

External beam then brachytherapy (48-50Gy)

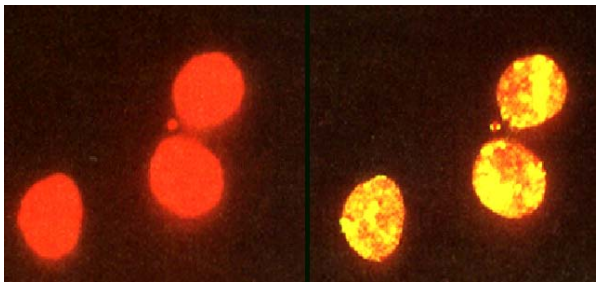
Acute and late normal tissue reactions scored

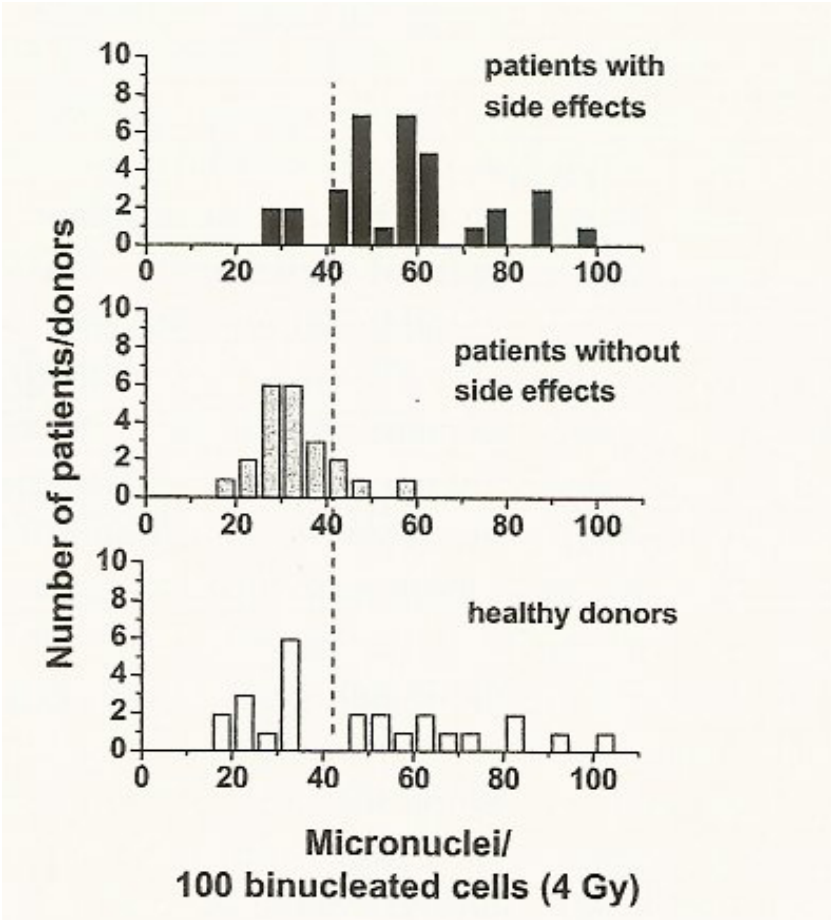
Correlated with MN (4Gy)

Note: variability in induced MN

Mean MN higher in acute reaction group

Significant overlap



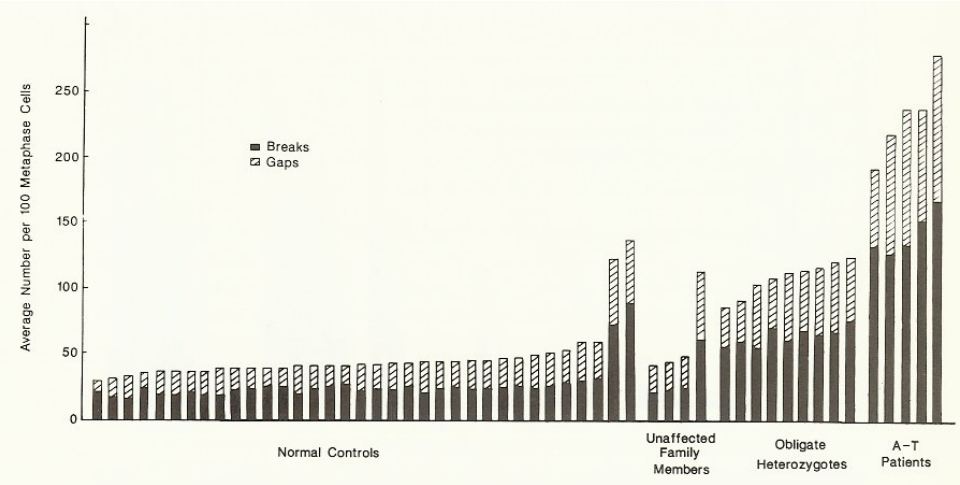


Widel et al., Radiation Res. 159, 713-721 (2003)

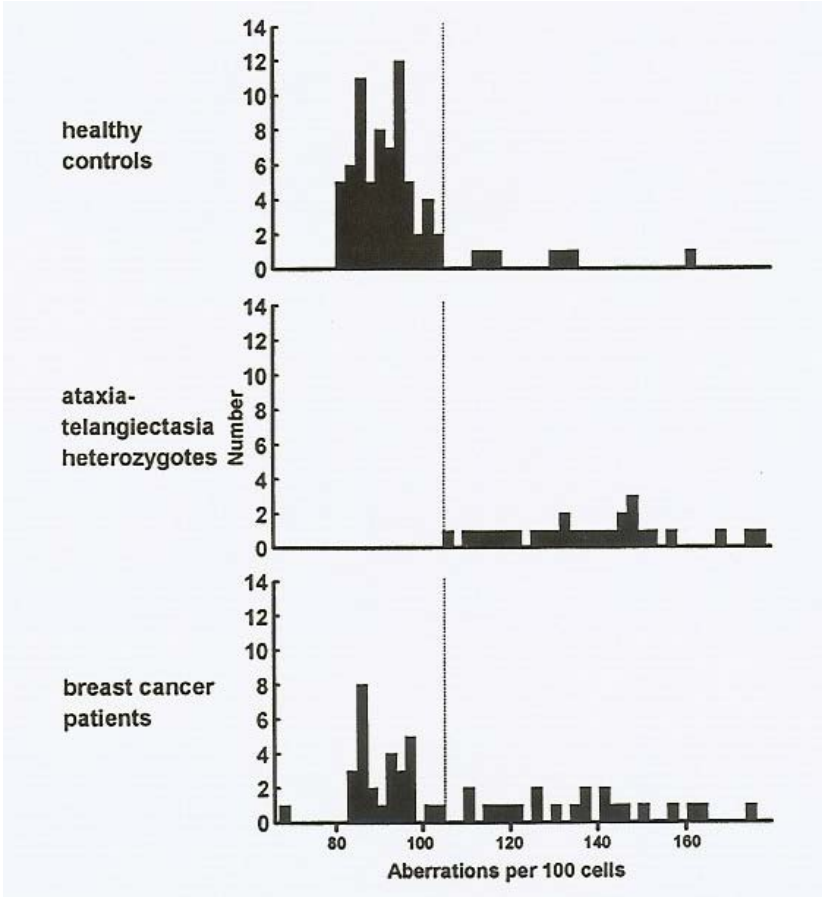
G_2 Chromosomal Radiosensitivity as a Biomarker

Contentious, but reproducible in a limited number of laboratories

Radio-sensitivity observed in a broad range of cancer-predisposing genetic disorders.



Parshad et al., PNAS 80, 5612-5616 (1983)



Scott et al., Lancet 244, 1444 (1994)

Later modified by Hsu et al to use Bleomycin in place of IR,
e.g., Hsu et al., Cancer Epi. Biomark. Prev. 1, 83-9, (1991)

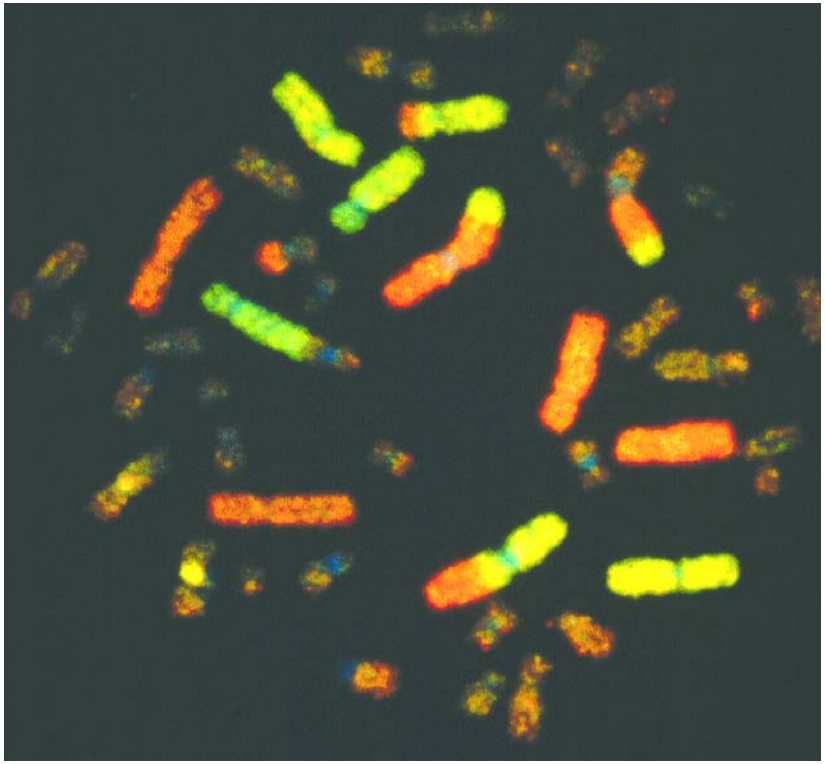
Three chromosome FISH as a biomarker for sensitivity [Neubauer et al., Radiation Res., 157, 312-321 (2002)]

Irradiate G_0 lymphocytes (0.7 or 2Gy)

Three chromosome painting Number of breakpoints/cell and number of long-lived stable aberrations

Identify AT and NBS +/-

Large EURATOM program - chromosomal aberrations**



Dr. J. Tucker

Carcinogenesis a Complex Disease

Most common variation in the genome is the single nucleotide polymorphism (SNP) occurring once every 300-500 nucleotides

Mapping complex traits requires determining which of the myriad of SNP's influence disease risk

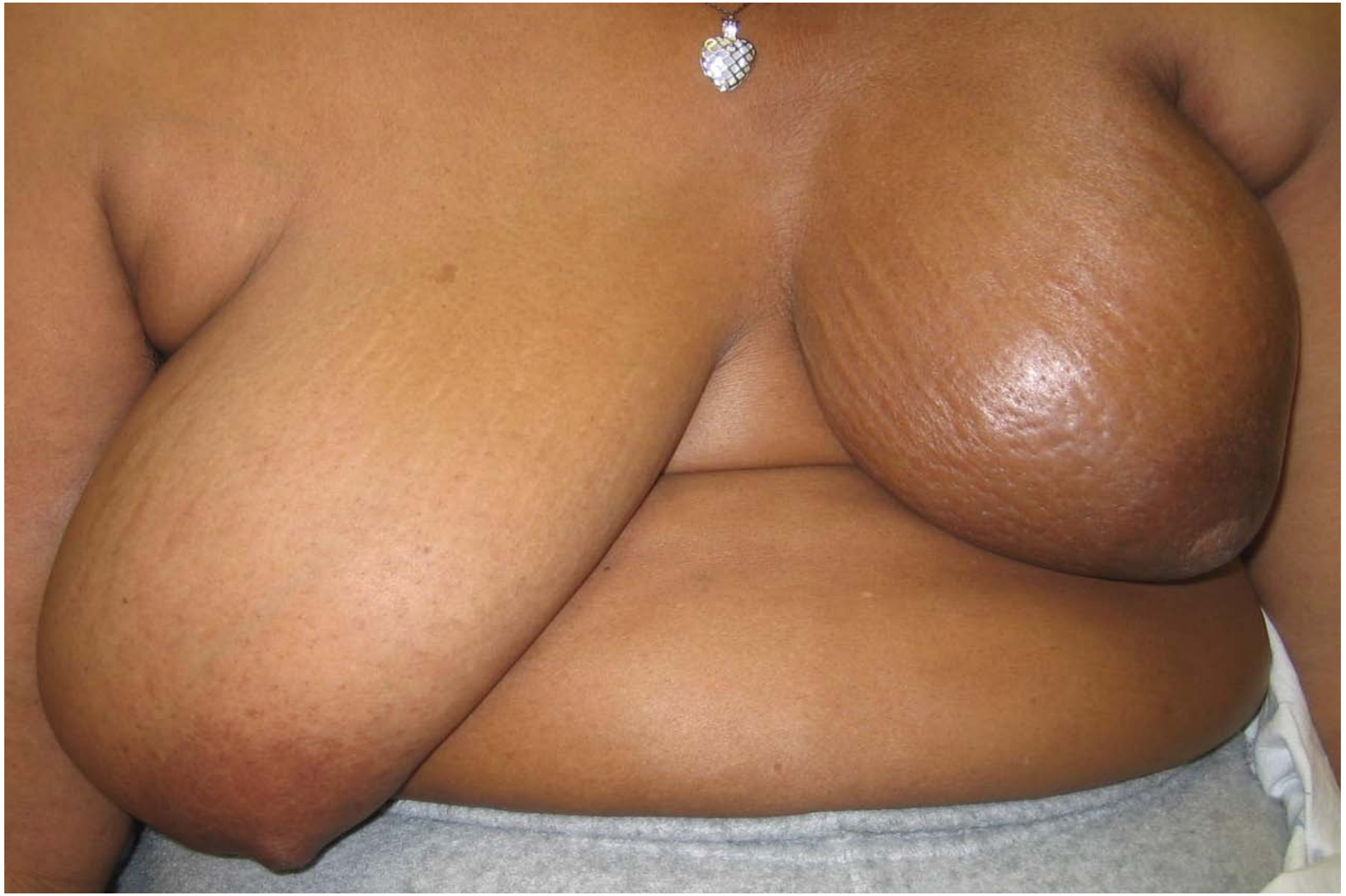
Technically feasible, but requires large population sample

Allelic variation in addition to haploinsufficiency

- inherent variability in expression
- epigenetics and regulatory control
- differential expression between alleles

Japanese in Japan versus in America

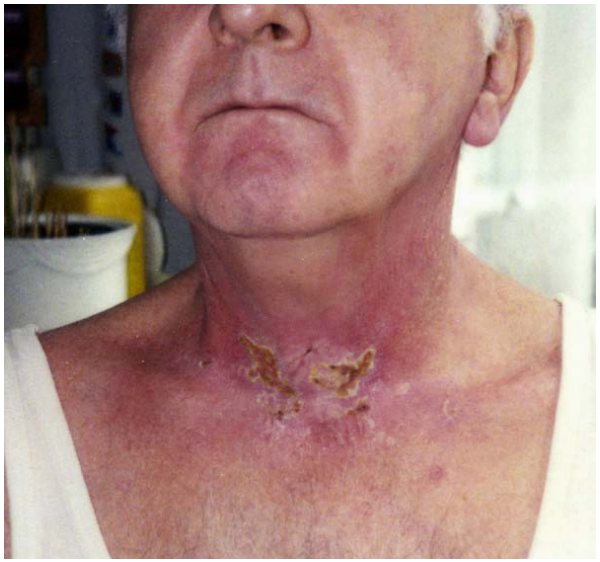
Gene - Gene as well as Gene - Environment interactions



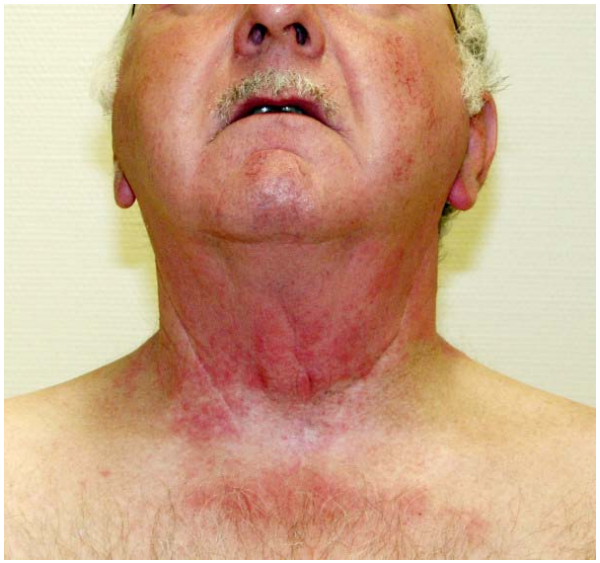
-Exaggerated breast fibrosis in African-American woman after breast-conserving therapy involving lumpectomy and whole-breast HIGH DOSE radiation**. Adverse clinical symptoms very rare.**

Radiation Recall Dermatitis (inflammatory reaction in a previously irradiated area)

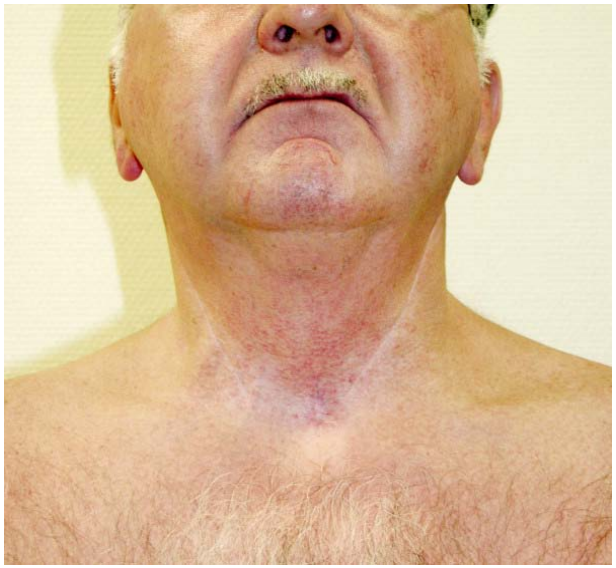
65 year old male with resected squamous cell carcinoma of the epiglottis
Adjuvant loco-regional RT (64.8Gy)
Patient took Hypericin during and after RT



Skin toxicity at the end of RT



Sunburn 1 year after RT



After stopping Hypericin

Putnik et al, *Radiation Oncology*, **1:**32 (2006)

So…..Where are we now then?

Epidemiological measures of risk based on large heterogeneous populations - thus a genetic contribution already included. Magnitude unknown, but acknowledged that its not uniformly distributed.

Technologies available to analyze genomic variation.

Data to date indicates some expected variation in cancer patients, e.g., DNA repair and cell cycle genes, but many not expected - complexity?

Application for radiotherapy patients (high dose exposures) v's occupational (protracted low doses)

Significant ethical, legal, social and economic considerations/implications

Comments and / or questions

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